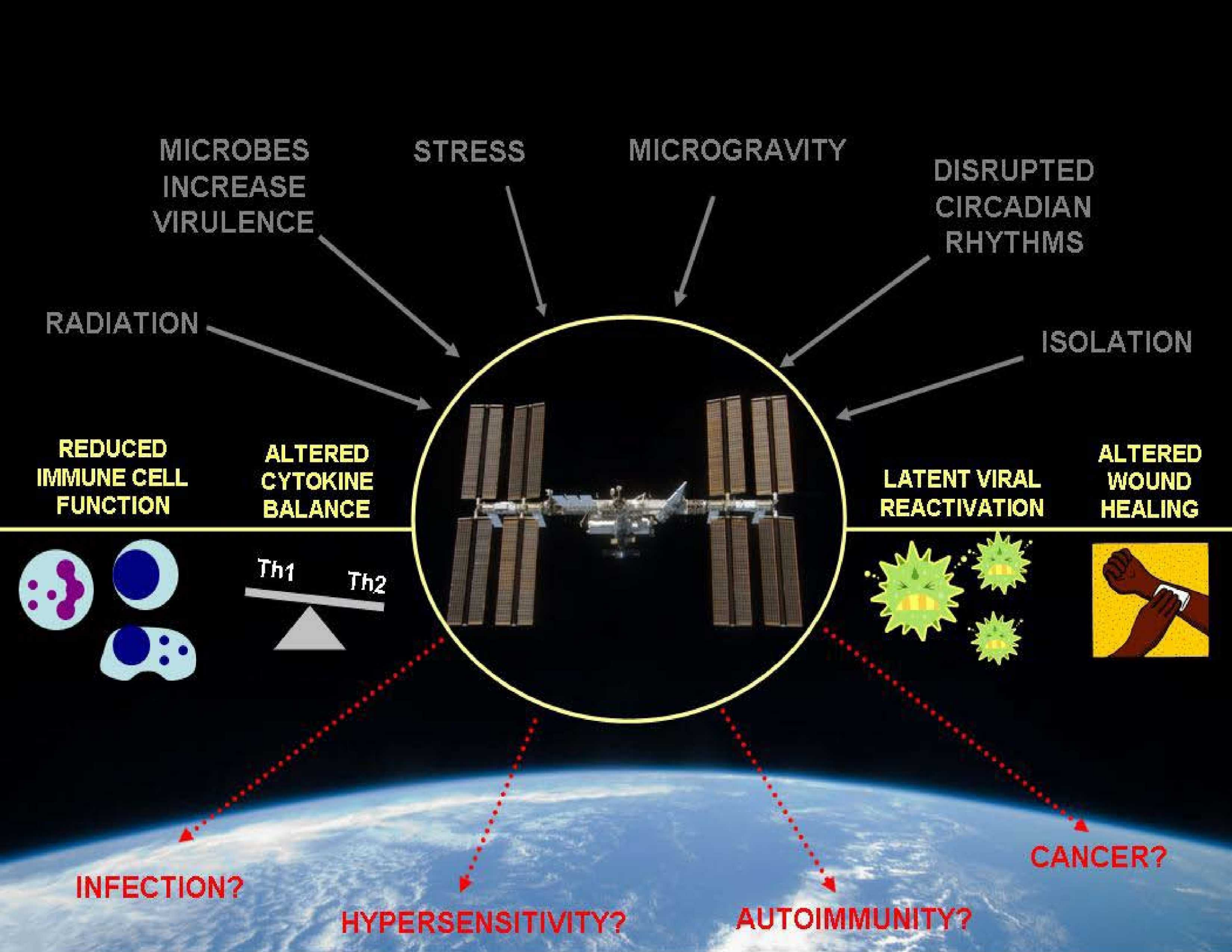
NASA HRP INVESTIGATORS MEETING

INTEGRATED IMMUNE

February 2010

Brian Crucian, Satish Mehta, Raymond Stowe, Peter Uchakin,
Heather Quiriarte, Duane Pierson and Clarence Sams


MICROBES INCREASE VIRULENCE
STRESS
MICROGRAVITY
DISRUPTED CIRCADIAN RHYTHMS
RADIATION
ISOLATION
REDUCED IMMUNE CELL FUNCTION
ALTERED CYTOKINE BALANCE
Th1
Th2
LATENT VIRAL REACTIVATION
ALTERED WOUND HEALING
INFECTION?
HYPERSENSITIVITY?
AUTOIMMUNITY?
CANCER?

JLB

Review

Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit?

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ABSTRACT

This year, we celebrate the 40th birthday of the first landing of humans on the moon. By 2020, astronauts should return to the lunar surface and establish an outpost there that will provide a technical basis for future manned missions to Mars. This paper summarizes major constraints associated with a trip to Mars, presents immunological hazards associated with this type of mission, and shows that our current understanding of the immunosuppressive effects of spaceflight is limited. Weakening of the immune system associated with spaceflight is therefore an area that should be considered more thoroughly before we undertake prolonged space voyages. *J. Leukoc. Biol.* 86: 1027–1038; 2009.

Introduction

In 1961, Yuri Gagarin became the first human to leave the confines of Earth. Since then, over 450 people have traveled into space, but so far, only 24 astronauts (those of the Apollo missions) have traveled beyond the first 400–500 km of the low-Earth orbit, in which the magnetic field of the Earth deflects a significant fraction of radiation. Beyond the Van Allen radiation belt, where charged particles are trapped in the magnetic field of the Earth, astronauts are exposed to solar and cosmic radiation.

On July 20, 1969, Neil Armstrong and Edwin Aldrin became the first humans to land on the moon. This summer, we celebrated the 40th birthday of this historic event. A few years ago, President George W. Bush proposed a manned return to the moon, with the moon to become the staging post for manned missions to Mars [1]. President Barack H. Obama's 2010 budget request, released on February 26, 2009, confirmed that NASA will stay on track to return to the moon by 2020. A mission to Mars and back will take a minimum of 520 days, of which roughly 1 month will be spent on the martian surface, and the rest will be spent in transit. At its furthest, the crew will be some 360 million km away from home. Consequently, astronauts will have to exercise an unprecedented level of autonomy and teamwork [2]. During the mission, they will experience not only microgravity but also various forms of stress, such as confinement, high expectations of performance, and risks of equipment failure or fatal mishaps. The enormous distance and long travel time to Mars will also probably affect the astronauts psychologically. The crew will therefore endure increased stress levels, radiation, as neither the moon nor Mars has magnetic fields or dense atmospheres that could attenuate them, and microgravity-induced changes, such as alterations in body fluid distribution, which could influence their immune system. As gravity has shaped the architecture of all biological systems on our planet, it is reasonable to observe aberrations in normal functioning of life in weightlessness. A long-term spaceflight will also pose a multitude of health risks, not only those associated with spaceflight, such as bone demineralization, skeletal muscle atrophy, and immune system suppression (**Fig. 1**), but also from common diseases that might cause specific problems under these circumstances. Another risk may be the development of pathogens in a closed environment, where air, food, waste, and water are recycled. Confinement of the crew during flight can and has resulted in the transfer of microorganisms among crew members [4, 5]. Finally, specific health risks might also be encountered on the lunar or martian surface, such as dust or chemicals that could irritate the respiratory tract, for example, or even new organisms. Indeed, 3 days on the moon during the final Apollo mission in 1972 left astronaut Eugene Cernan weary and filthy with rock dust. A trip to Mars will certainly multiply the hazards of space travel.

Humans are ready to accept great risks to go where no one has gone before, but do we have sufficient and sound biologi-

Abbreviations: AHCC=active hexose correlated compound, CNES=French National Space Center, ESA=European Space Agency, Ets=E26 transformation specific, HDBR=head-down bed-rest, ML-2=International Microgravity Laboratory 2, ISS=International Space Station, PKA/PKC=protein kinase A/C, respectively, PMN=polymorphonuclear neutrophil, ROS=reactive oxygen species, SLS-1=Spacelab Life Sciences 1

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Human Research Program
Human Health Countermeasures Element

Evidence Book

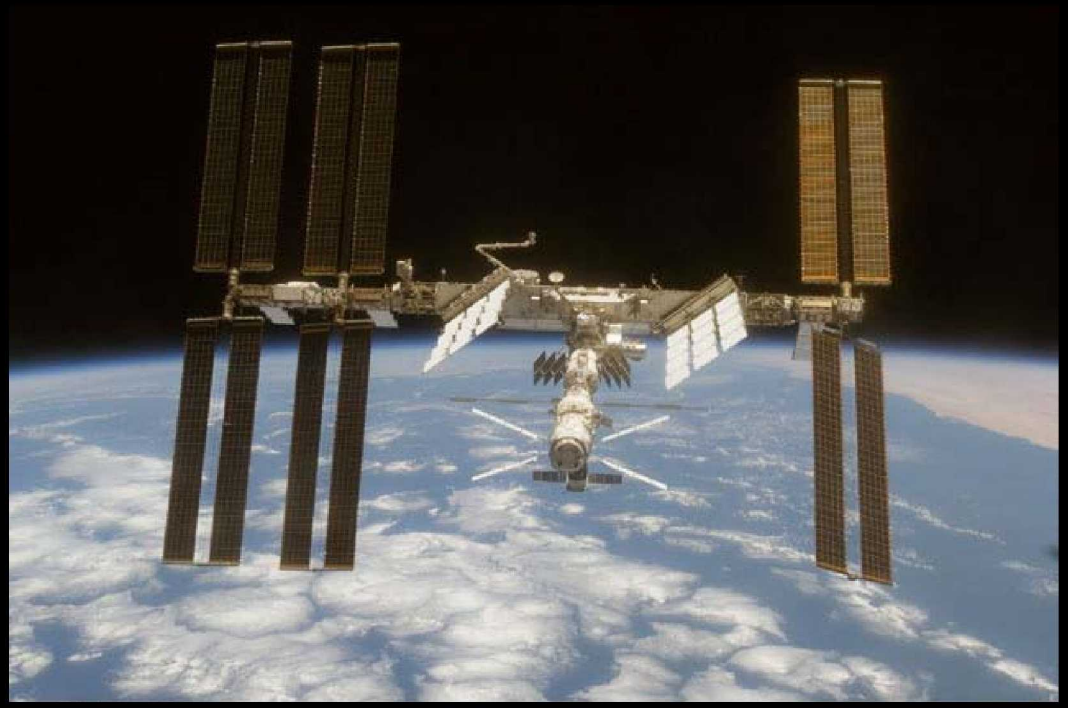
Risk of Crew Adverse Health Event Due to Altered Immune Response

June 2009

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

http://humanresearch.jsc.nasa.gov/elements/smo/hrp_evidence_book.asp

Objectives

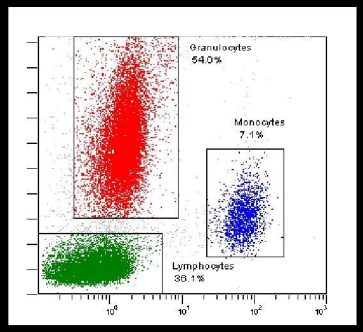


- Replace several recent immune studies with one comprehensive study that will include in-flight sampling.
- Address lack of in-flight data: determine the in-flight status of immunity, physiological stress, viral immunity/reactivation (short/long).
- Determine the clinical risk related to immune dysregulation for exploration class spaceflight.
- Determine the appropriate monitoring strategy for spaceflight-associated immune dysfunction, that could be used for the evaluation of countermeasures.

Assays for ***Integrated Immune***

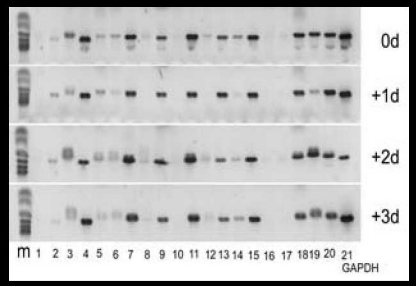
JSC Immunology Laboratory

- Leukocyte subsets
- T cell function
- Intracellular/secreted cytokine profiles



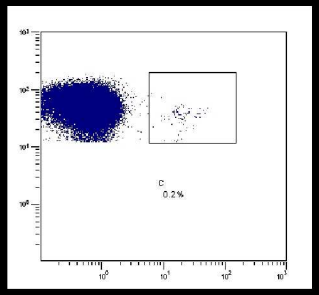
Mercer University

- Plasma cytokine balance
- Leukocyte cytokine RNA



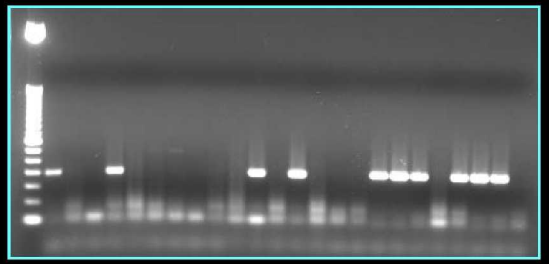
Microgen Laboratories

- Virus specific T cell number
- Virus specific T cell function
- Plasma stress hormones



JSC Microbiology Laboratory

- Latent herpesvirus reactivation (saliva/urine)
- Saliva/urine stress hormones
- Circadian rhythm analysis



Subjects

Study ‘n’:	17 Short duration
	17 Long duration
Completed:	18 Short duration
	8 Long duration

Today:
Completed Short Duration Data

9 Shuttle missions; 18 Shuttle crewmembers participated

JSC Immunology Laboratory

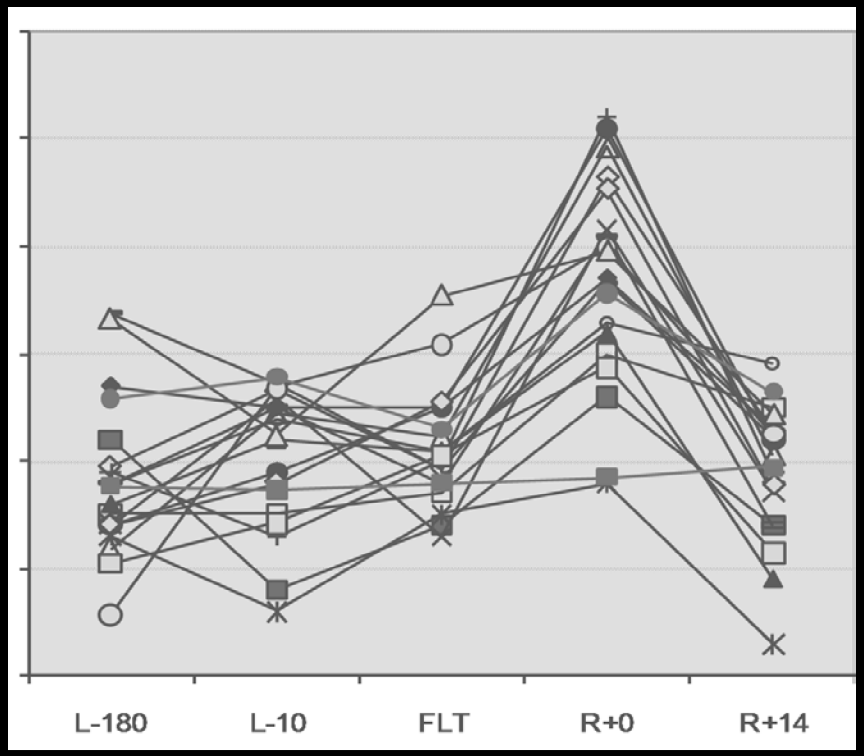
-Peripheral leukocyte distribution

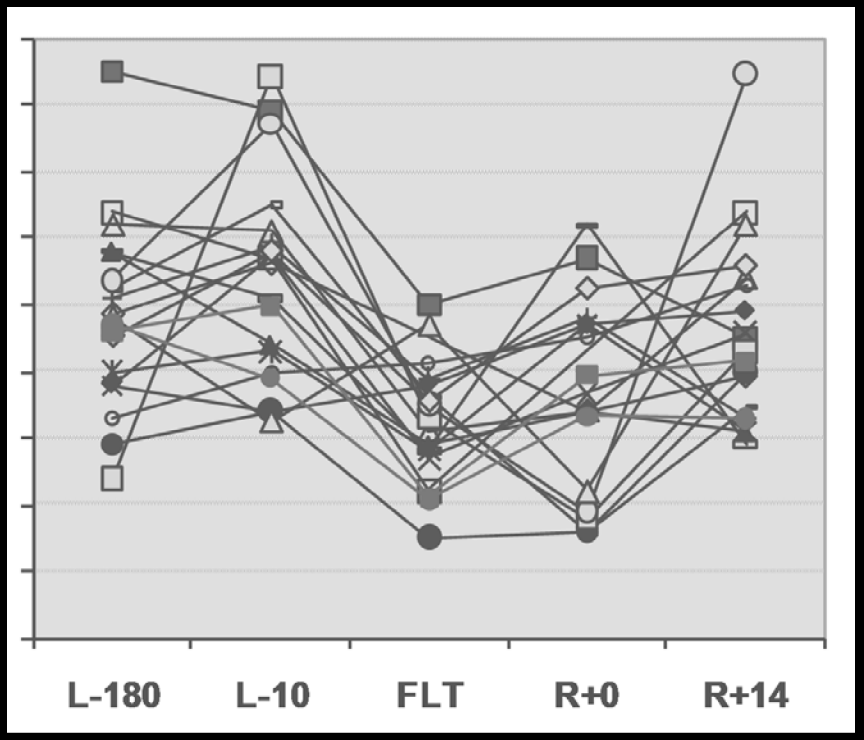
-T cell function

-Intracellular cytokine profiles

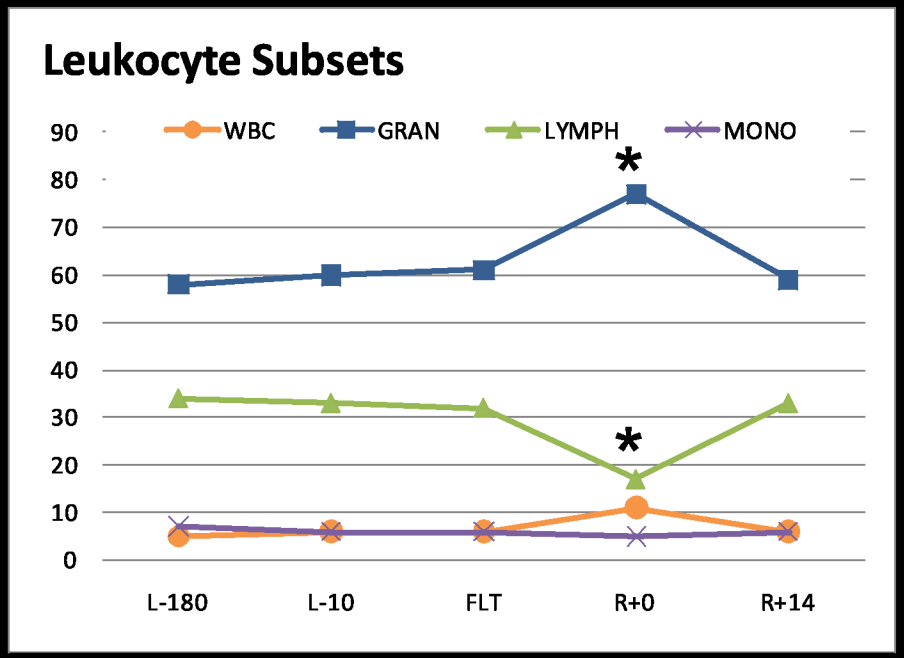
-Secreted cytokine profiles

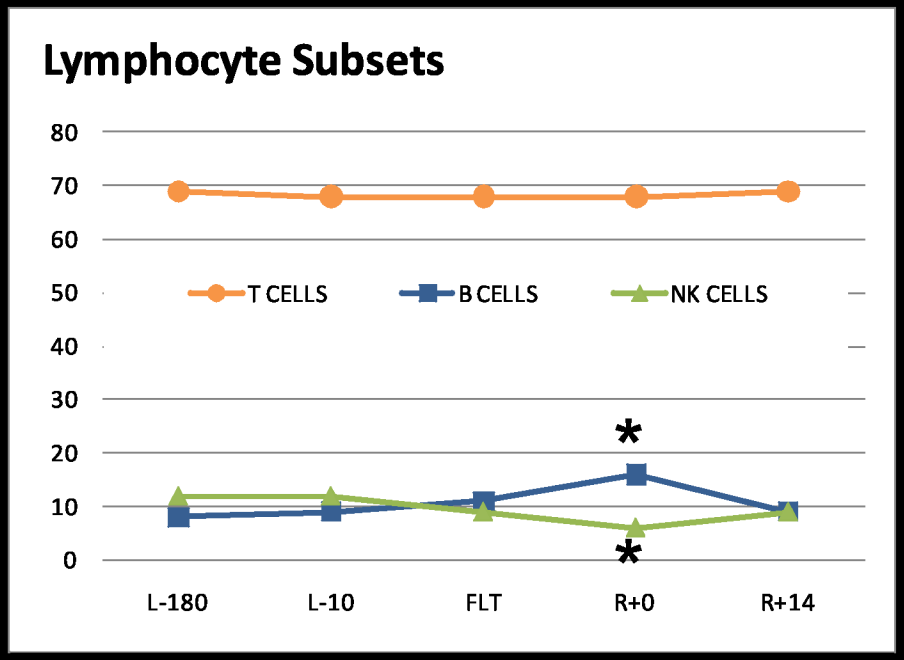
Representative Individual Data



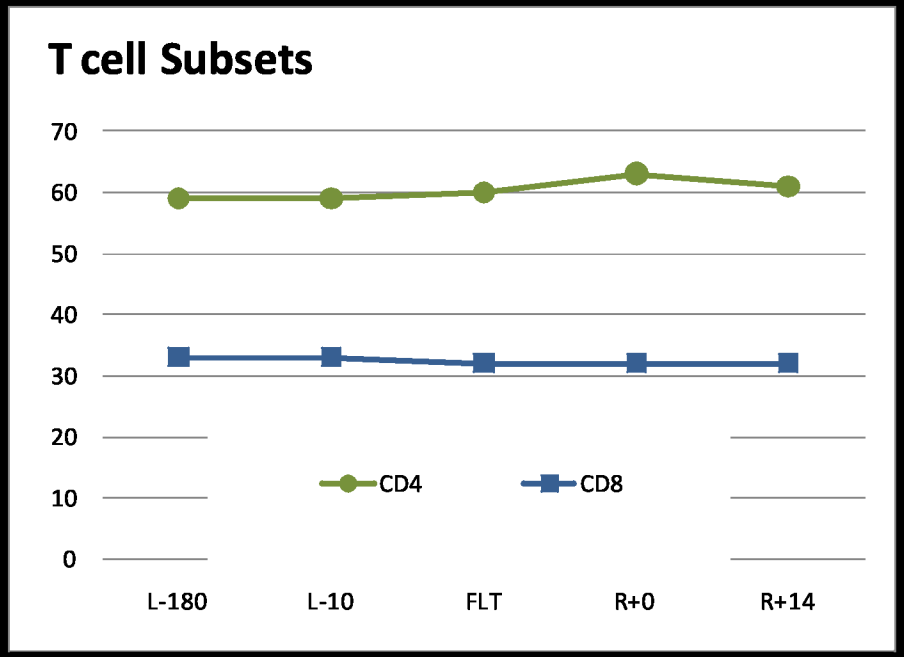


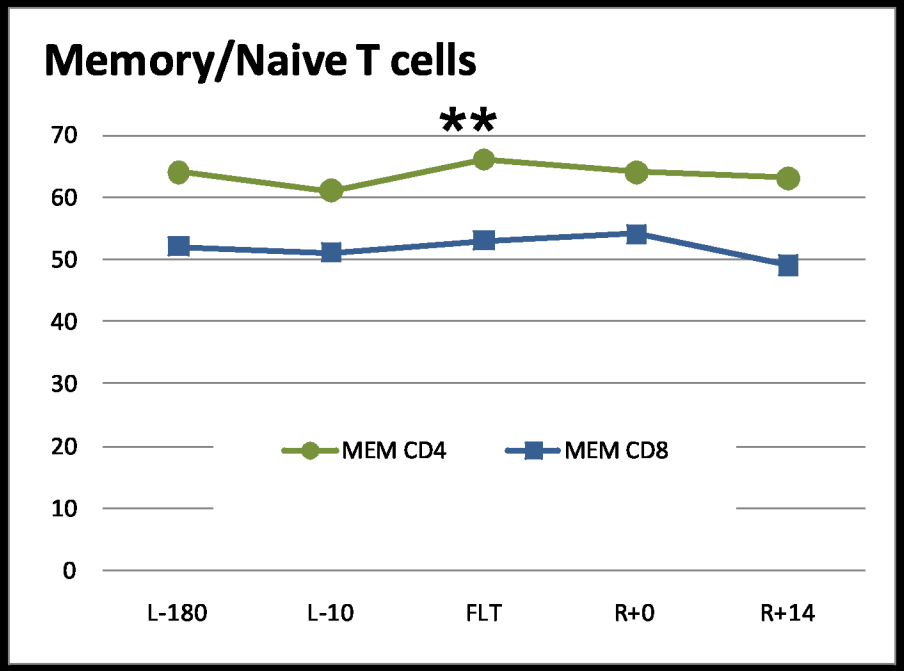
Peripheral Leukocyte Distribution



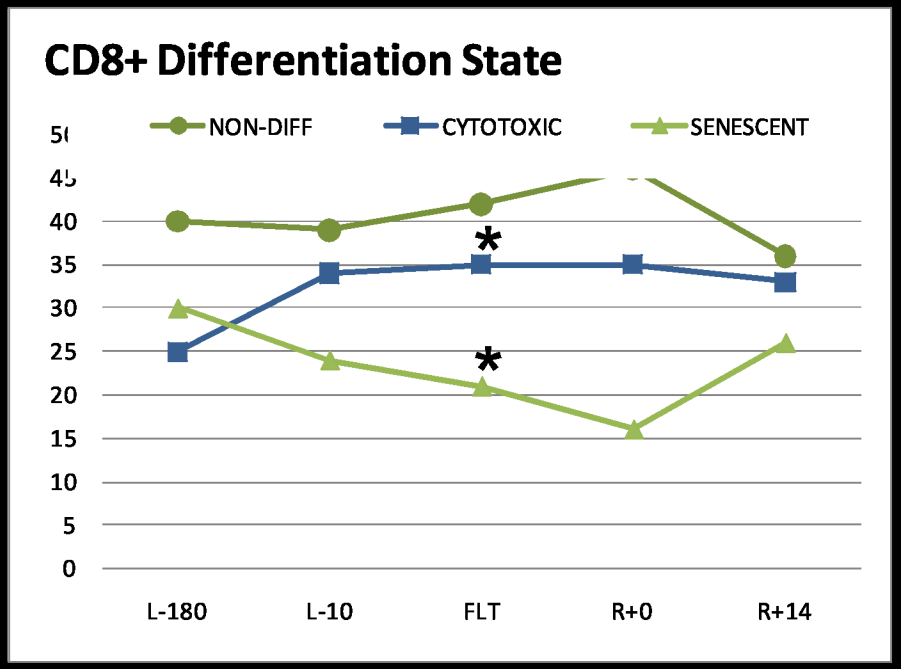


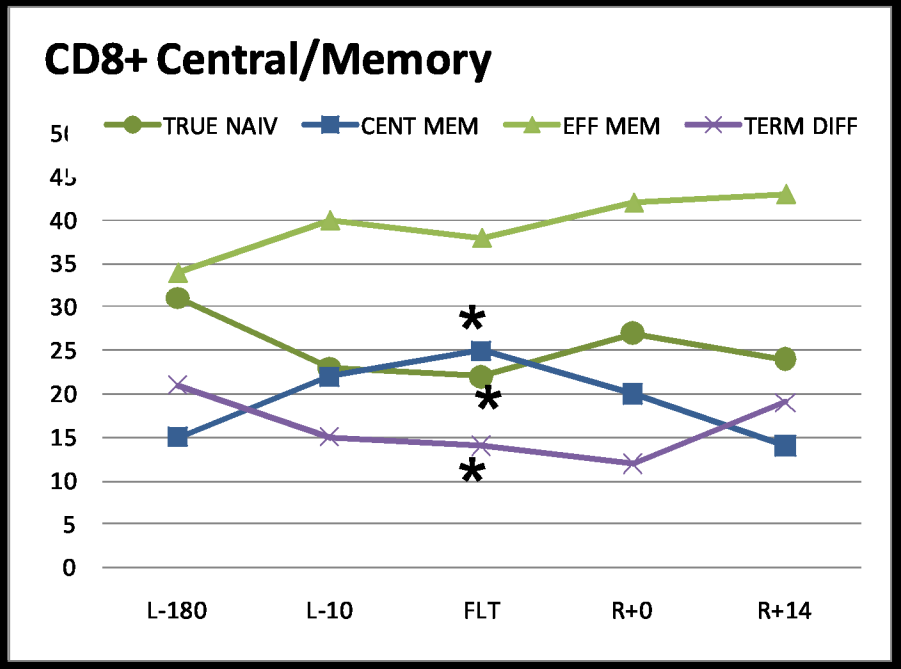
Peripheral Leukocyte Distribution



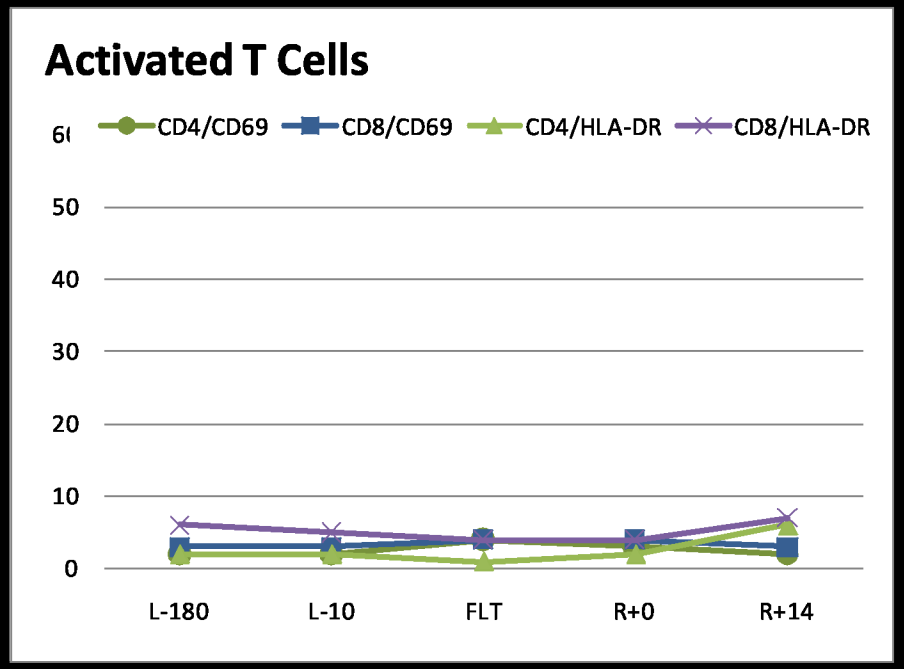


Peripheral Leukocyte Distribution



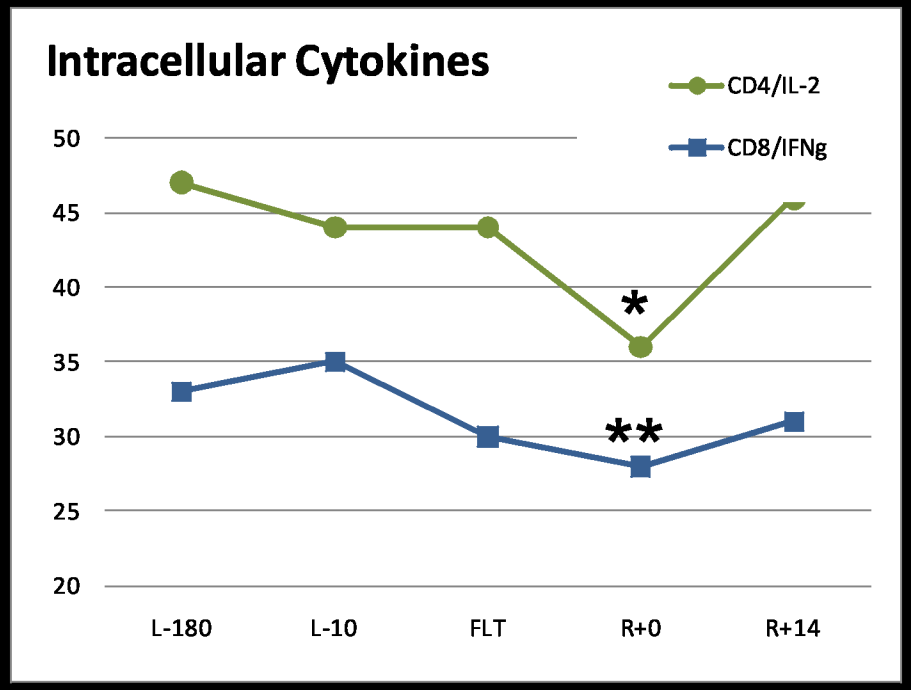


Peripheral Leukocyte Distribution

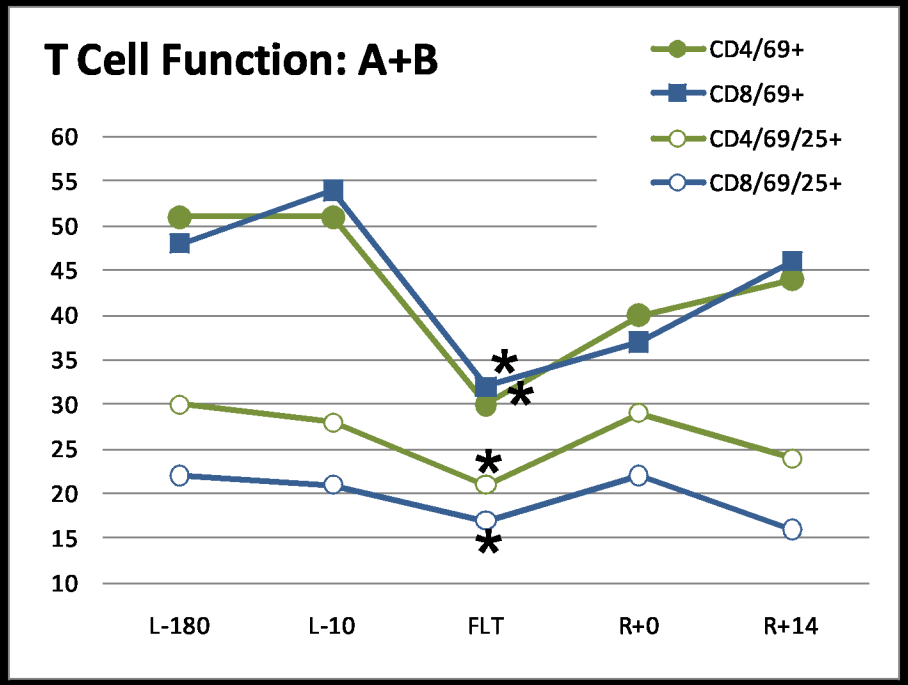


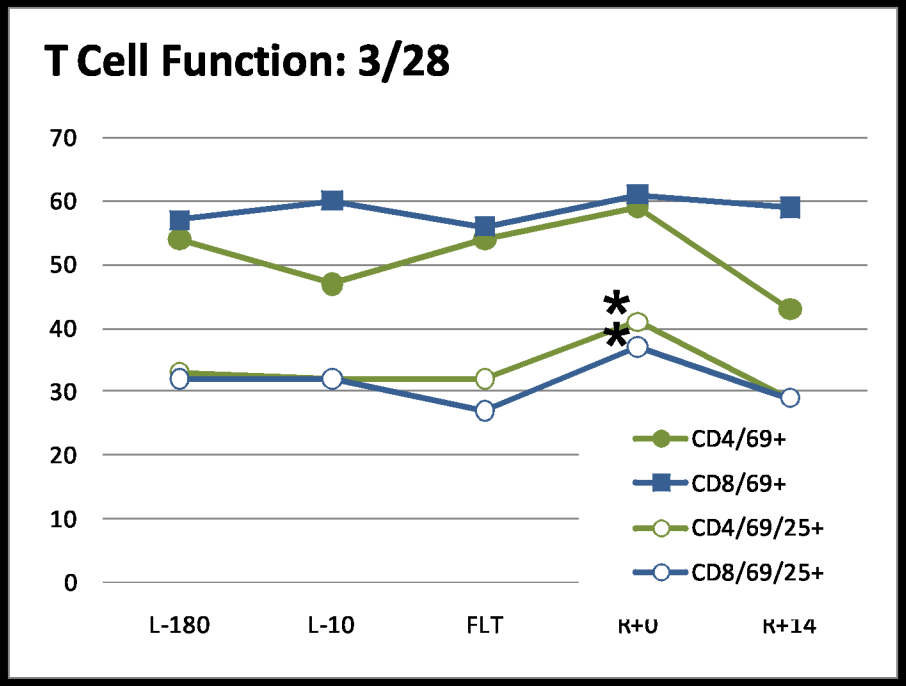
T Cell Function:

Intracellular Cytokine Profiles

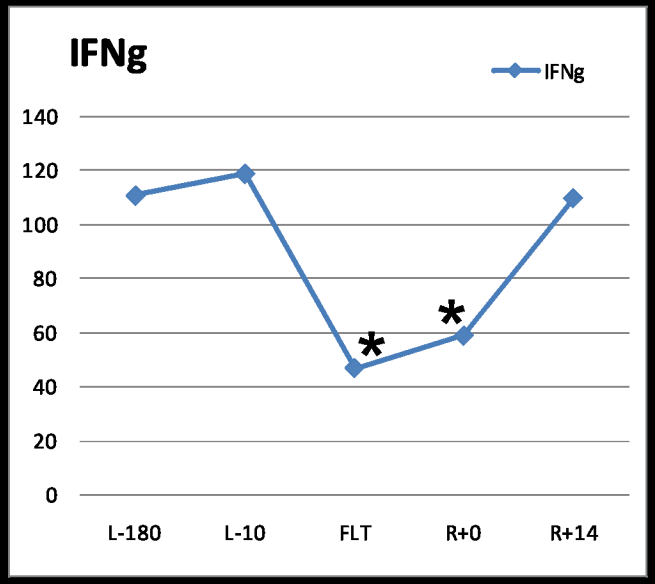


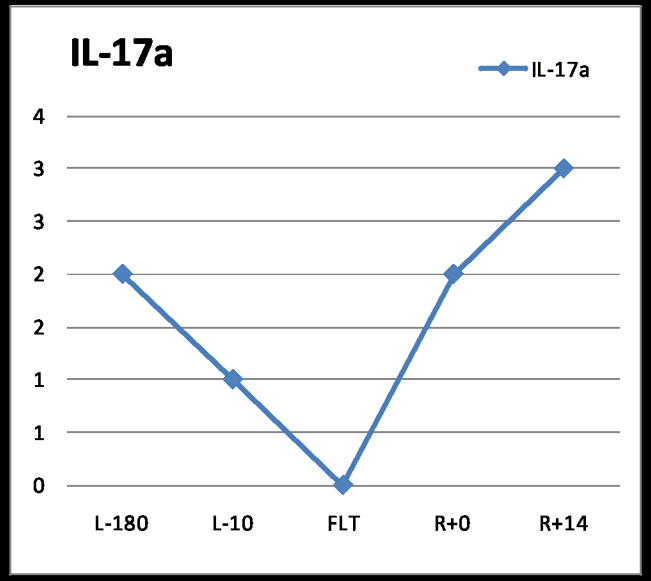
T Cell Function; 24 hr culture

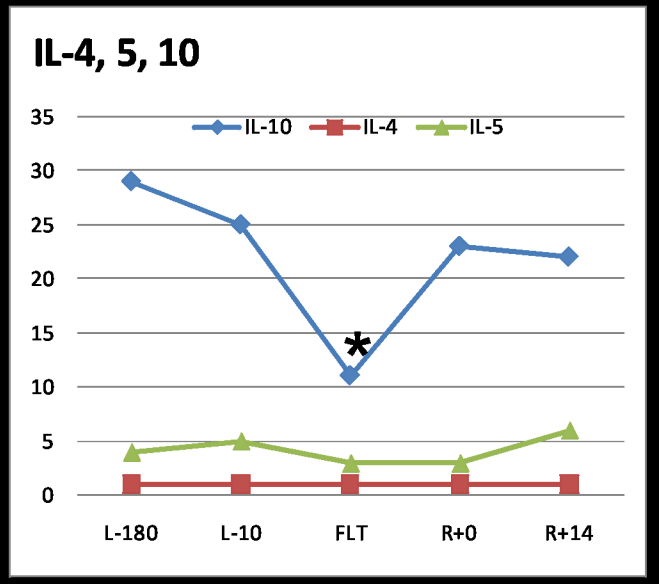


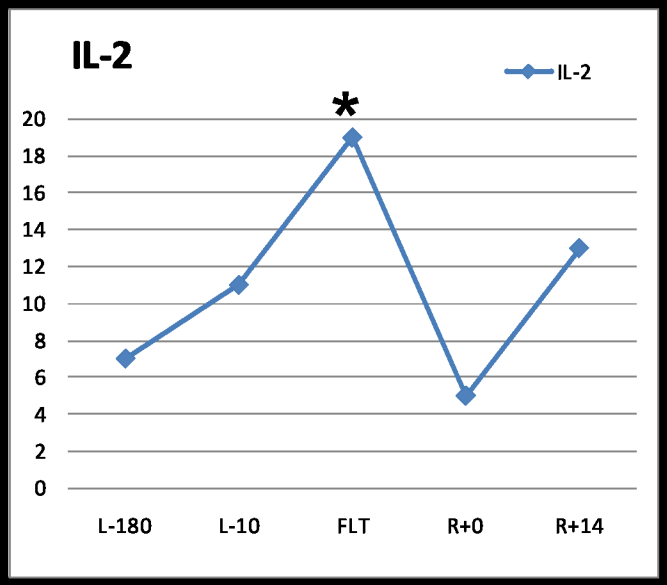


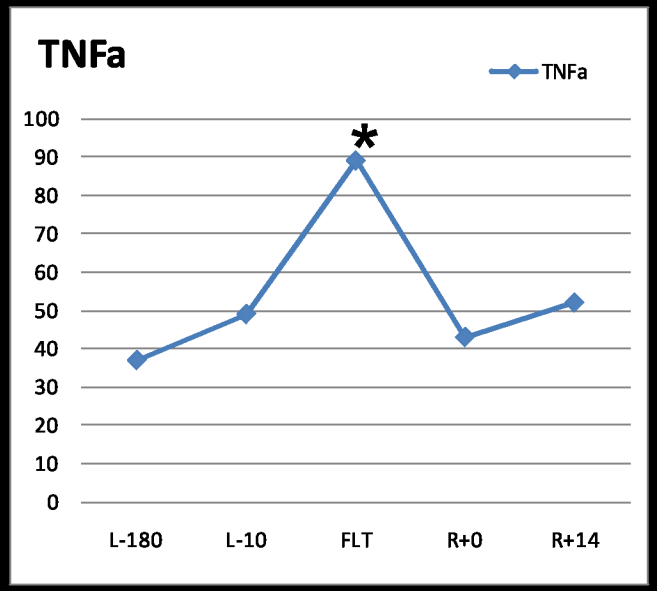
T Cell Function:
Secreted Cytokine Profiles (CD3/CD28 48hr)

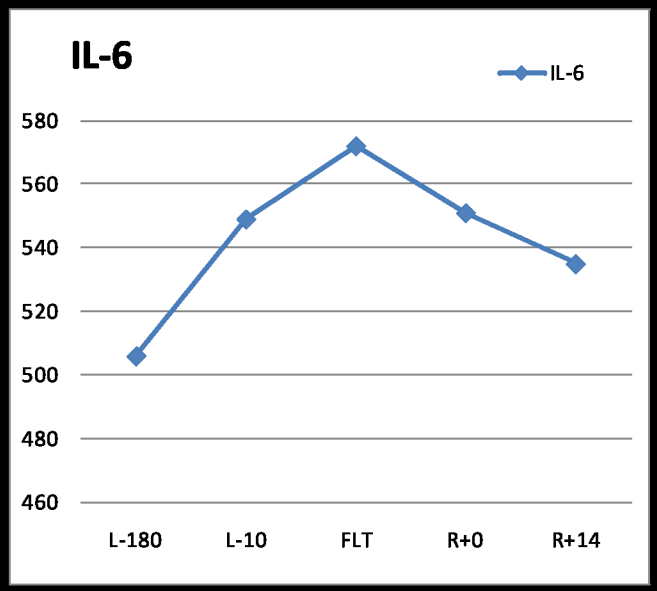




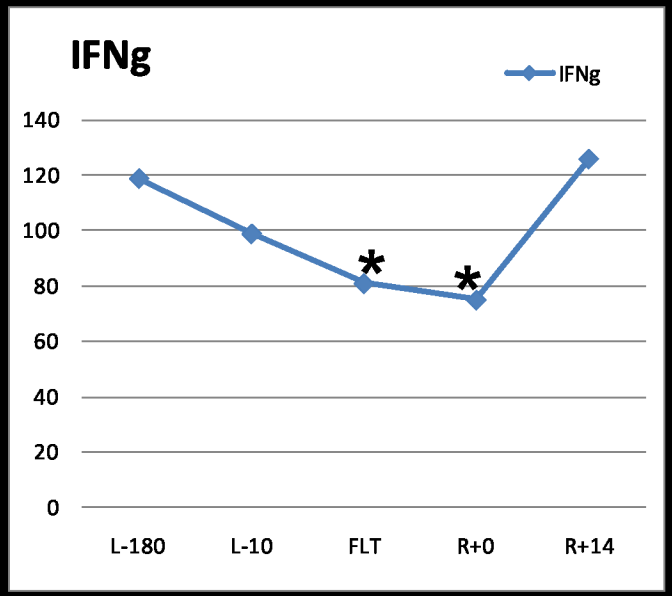


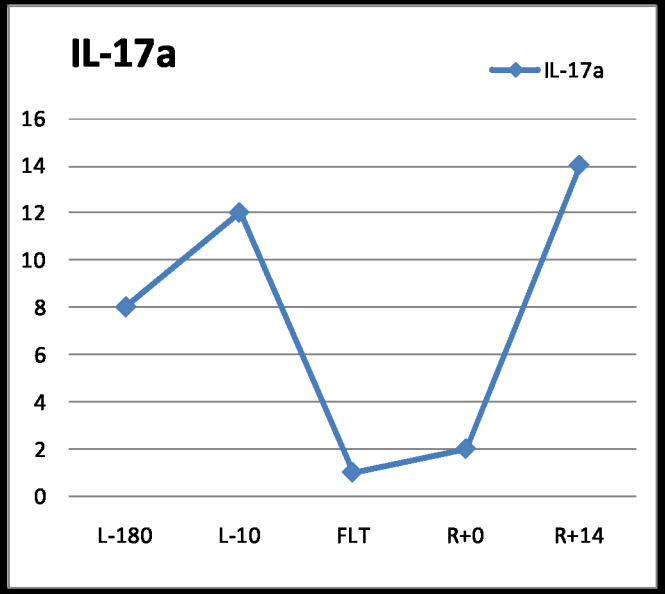


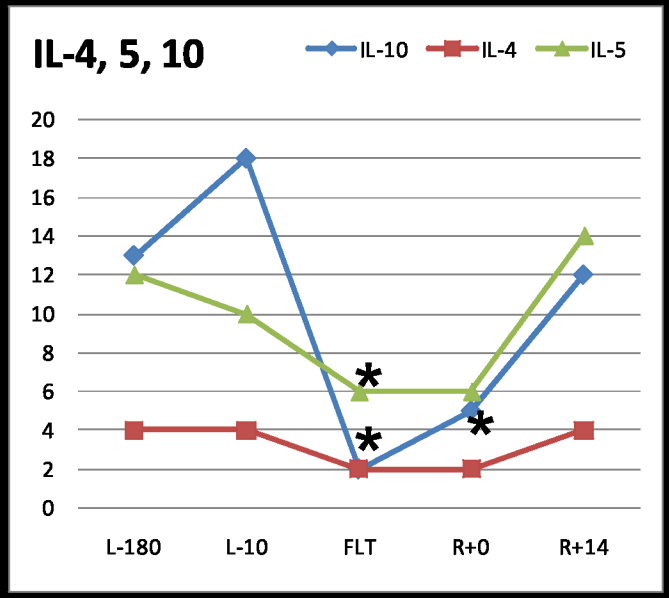


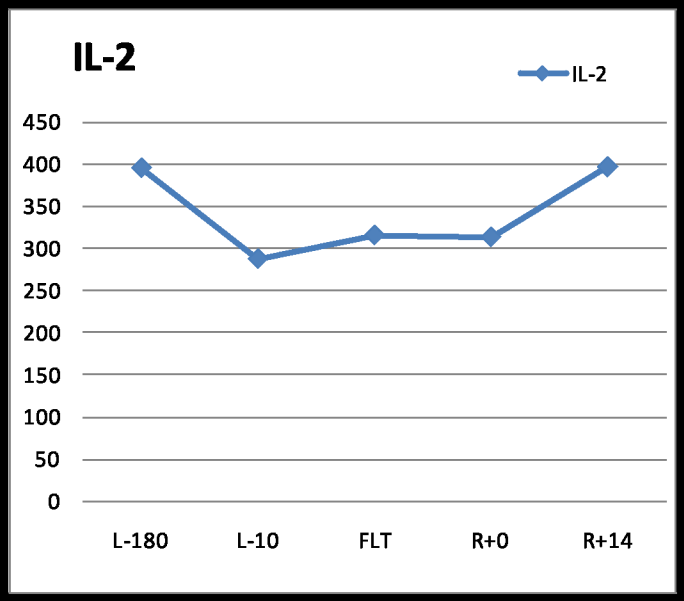


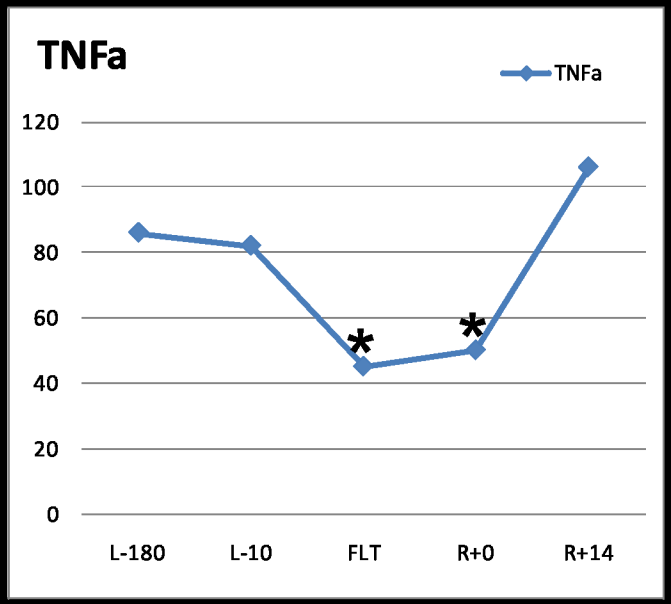
T Cell Function:
Secreted Cytokine Profiles (PMA+I 48hr)

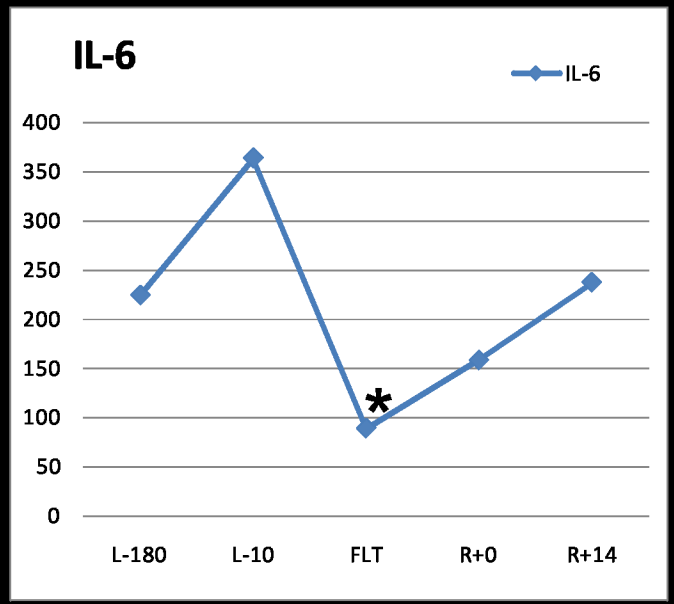




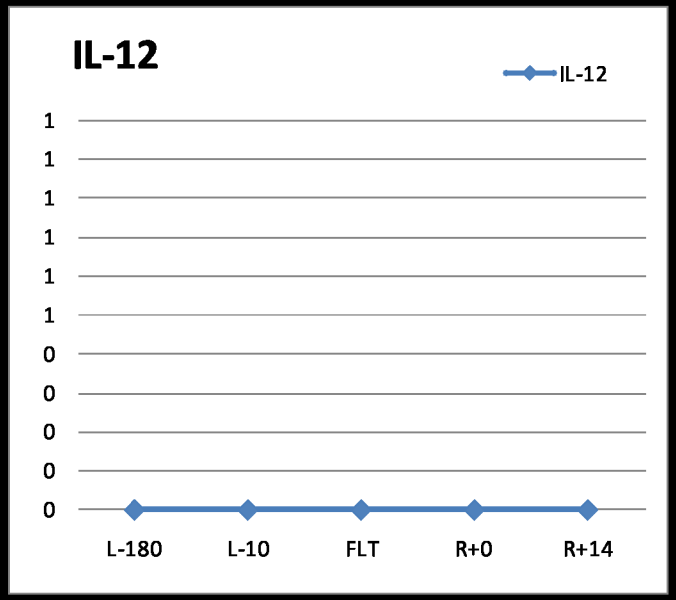


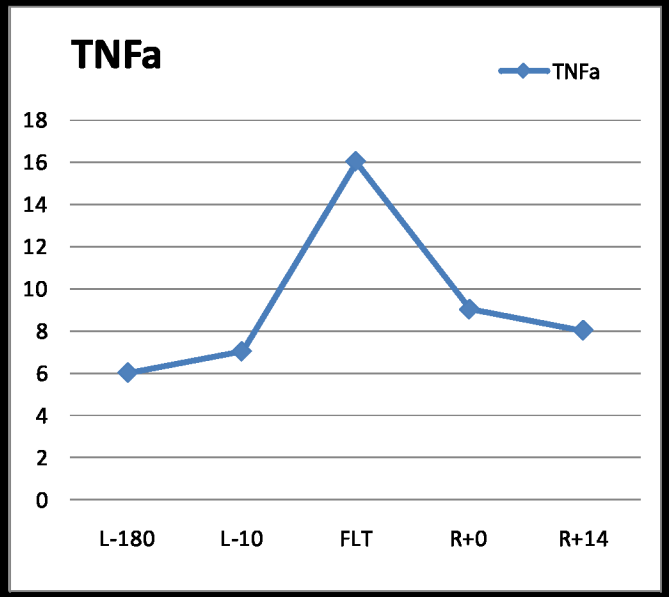


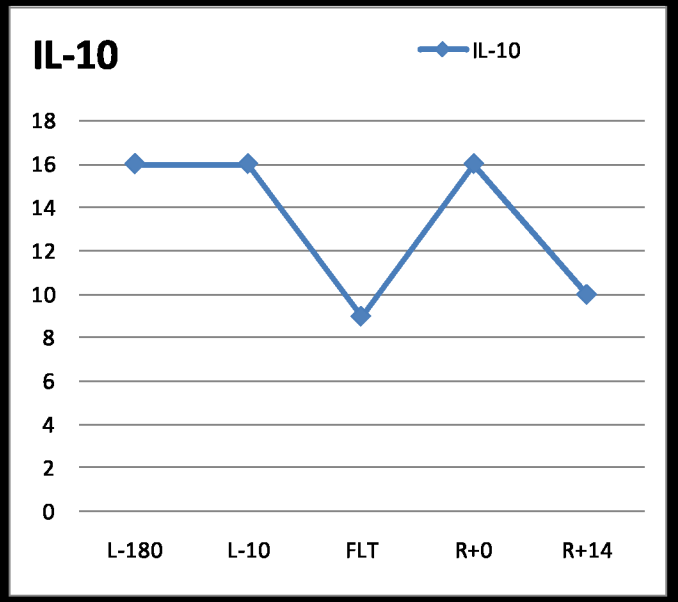


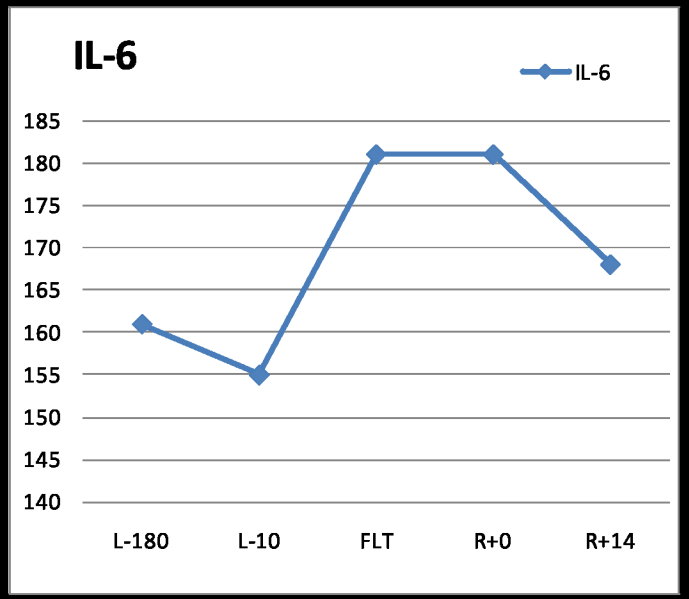


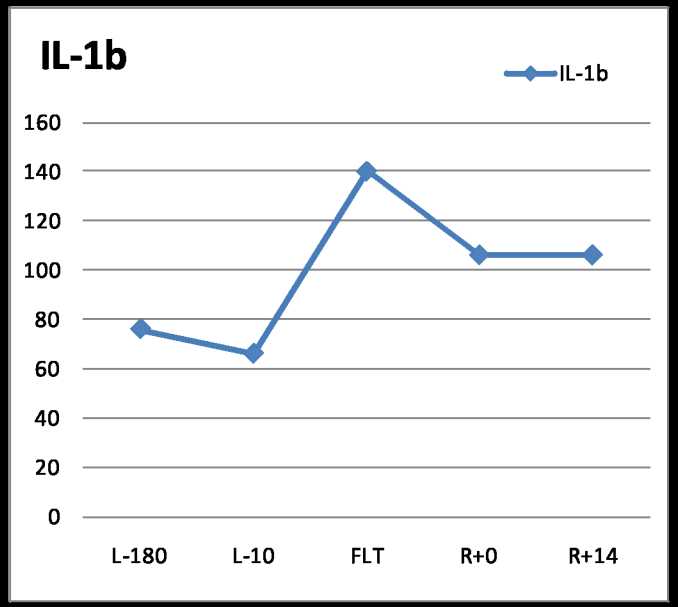
Innate Immune Function:
Secreted Cytokine Profiles (LPS 48hr)

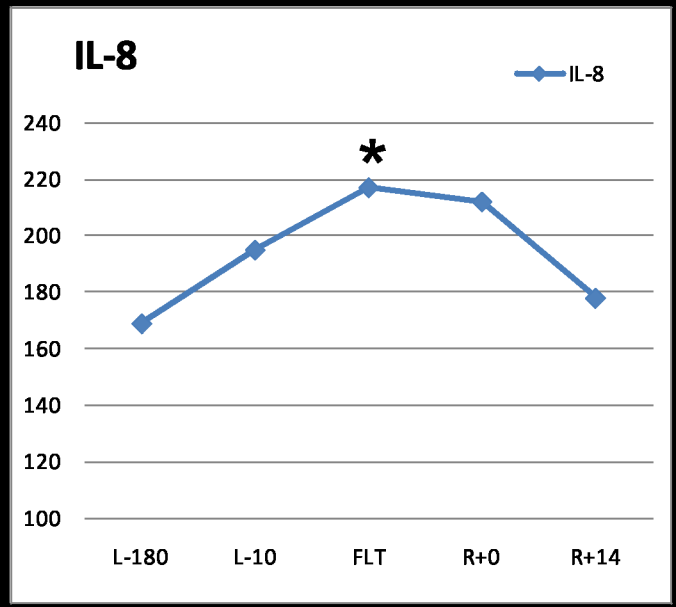










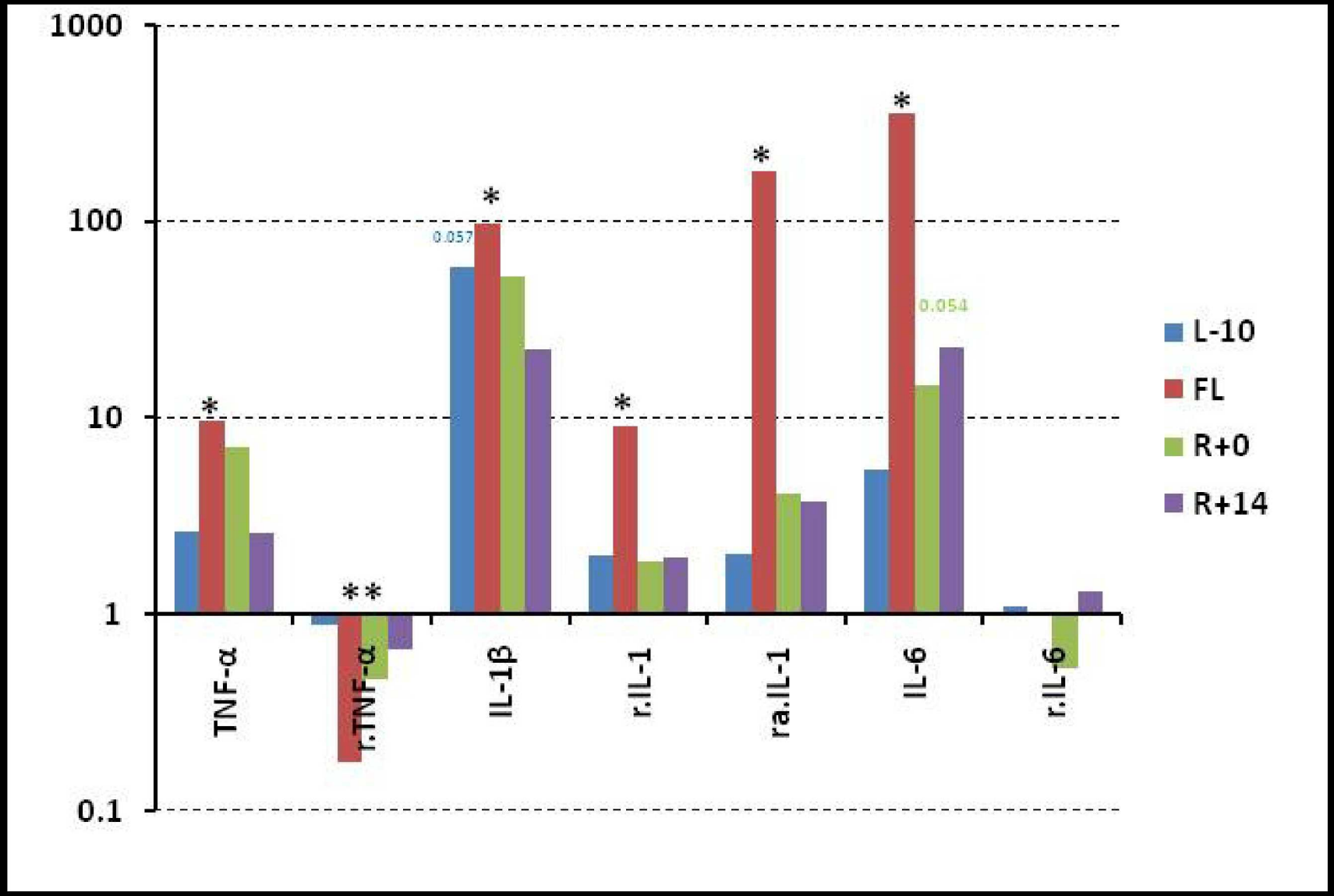


Mercer University

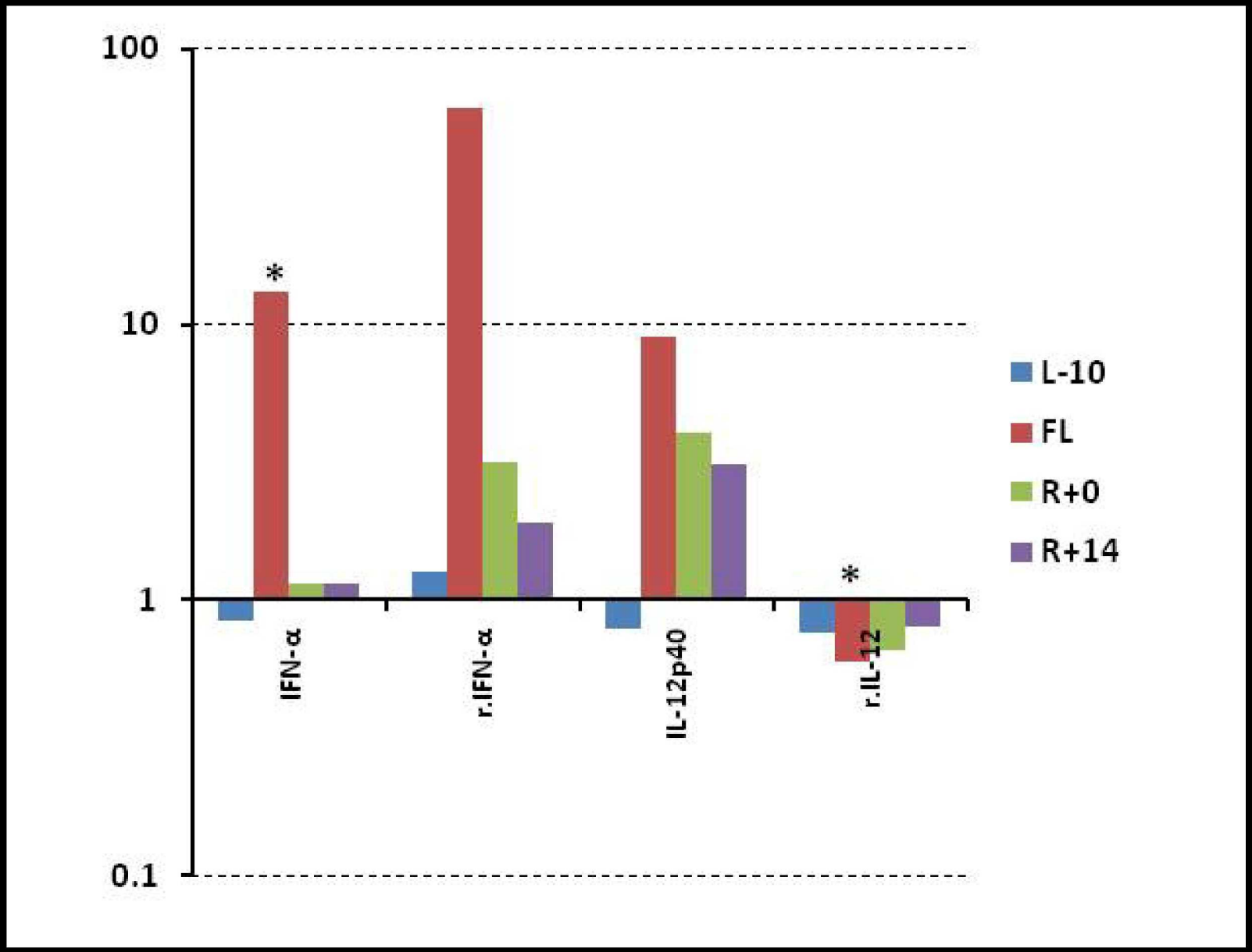
-Leukocyte cytokine mRNA

-Plasma cytokine levels

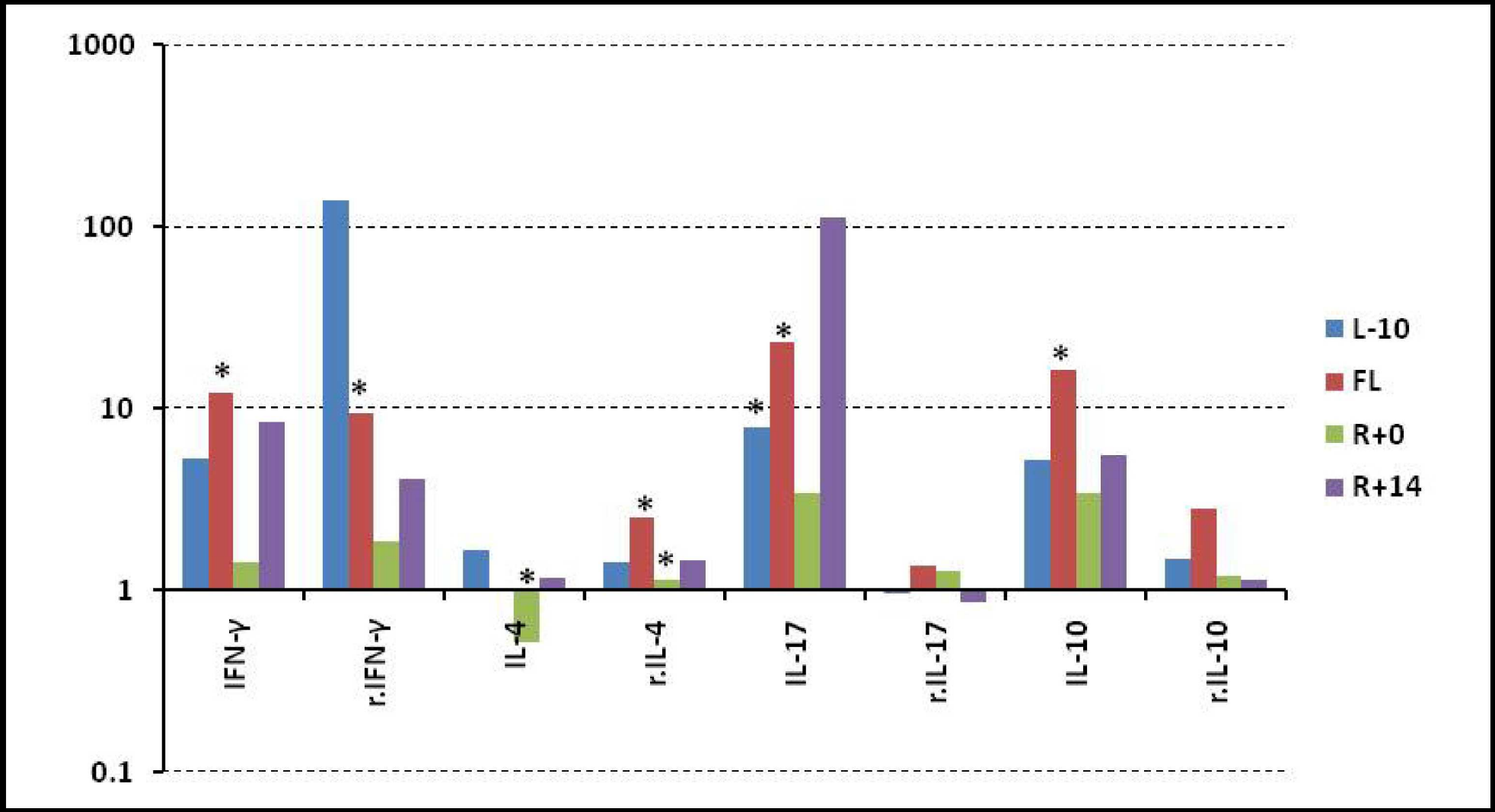
Cytokine mRNA:
INFLAMMATORY RESPONSE. Mean, n=11.



Cytokine mRNA:
INNATE ANTI-VIRAL IMMUNITY. Mean, n=11.



Cytokine mRNA:
ADAPTIVE IMMUNE RESPONSE - Regulatory Th1-Th2-Th17-Treg paradigm.



Microgen Laboratories

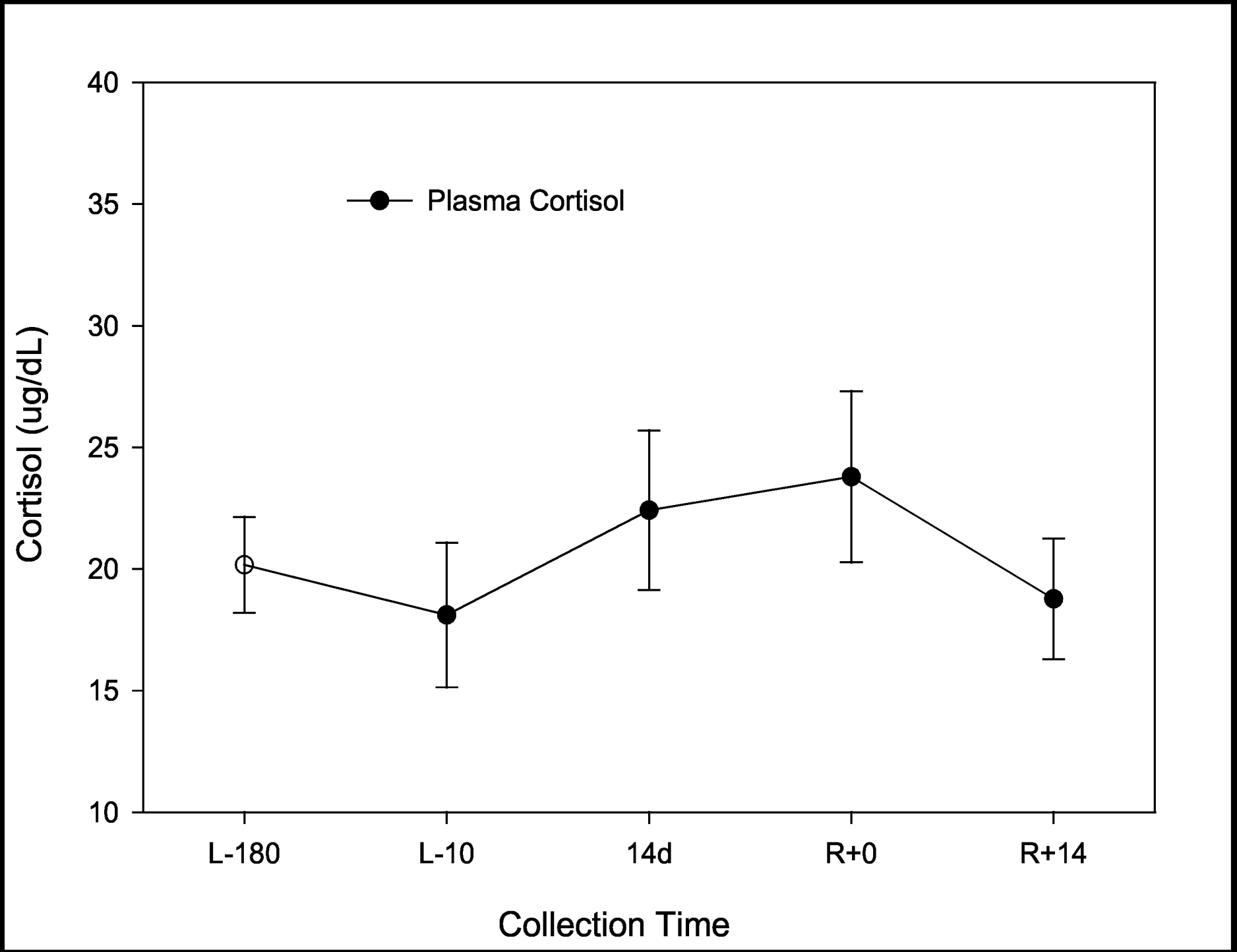
-Virus specific T cell number

-Virus specific T cell function

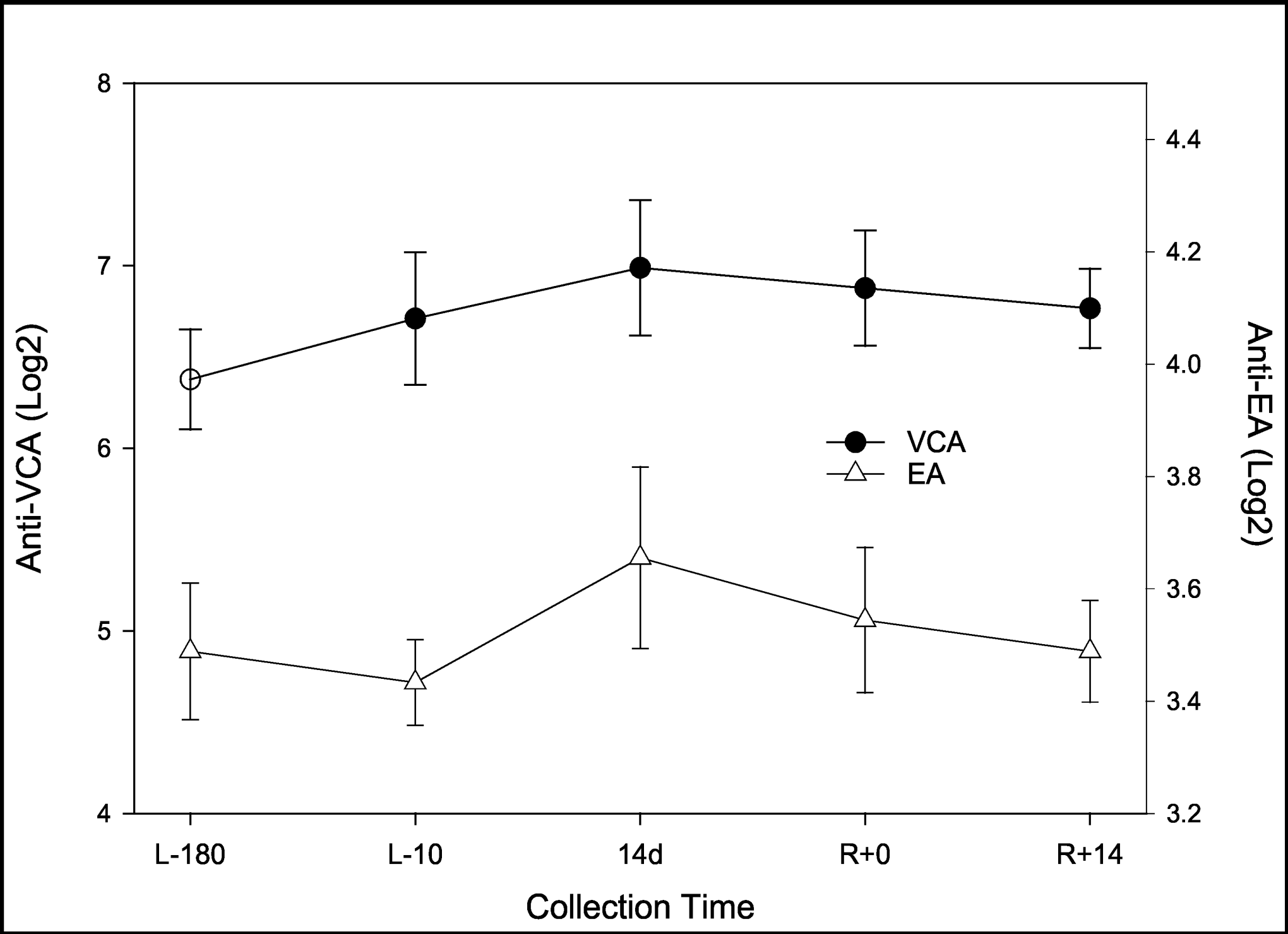
-B cell EBV copy level

-Stress hormone levels (plasma)

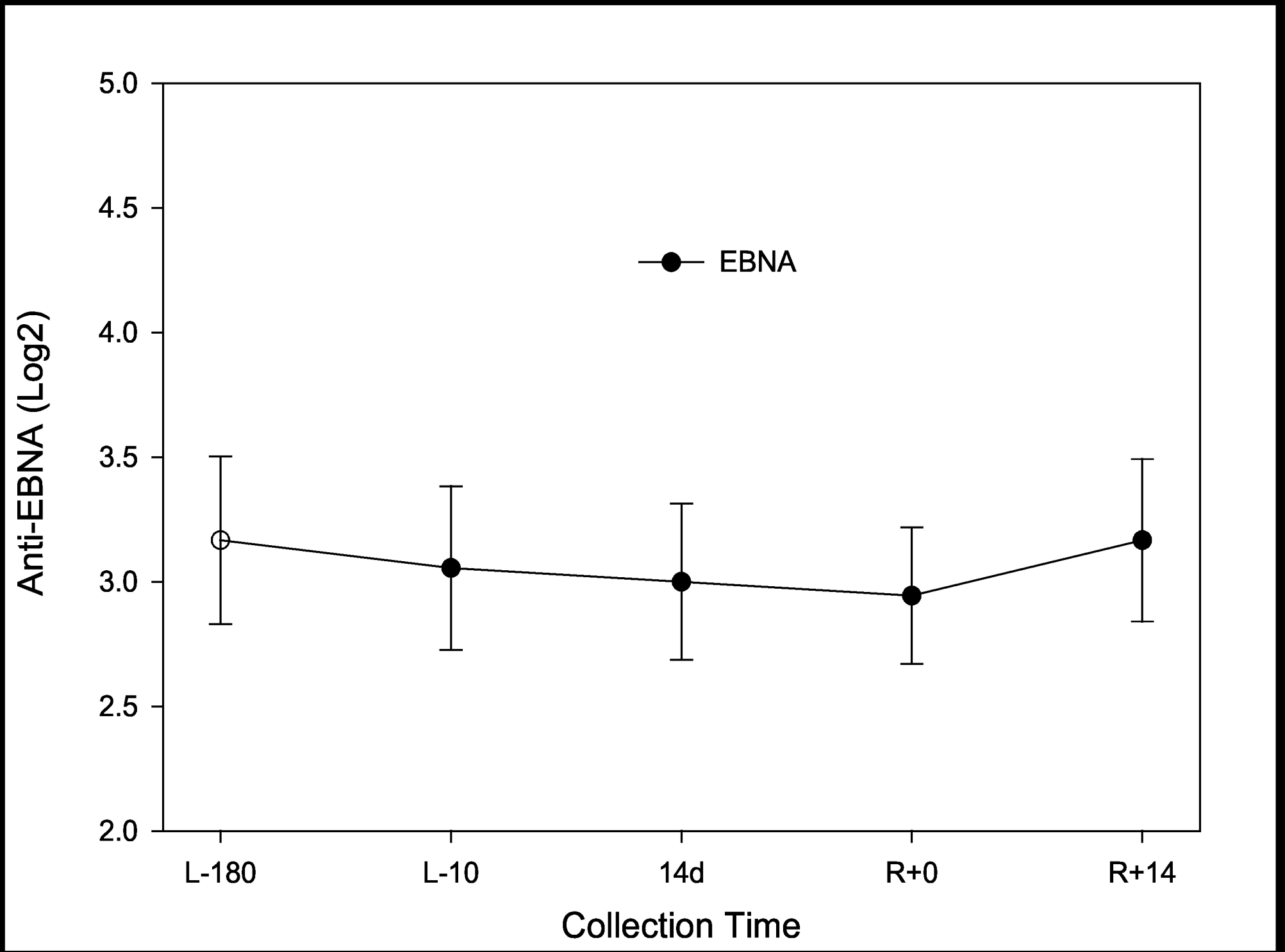
Plasma cortisol levels



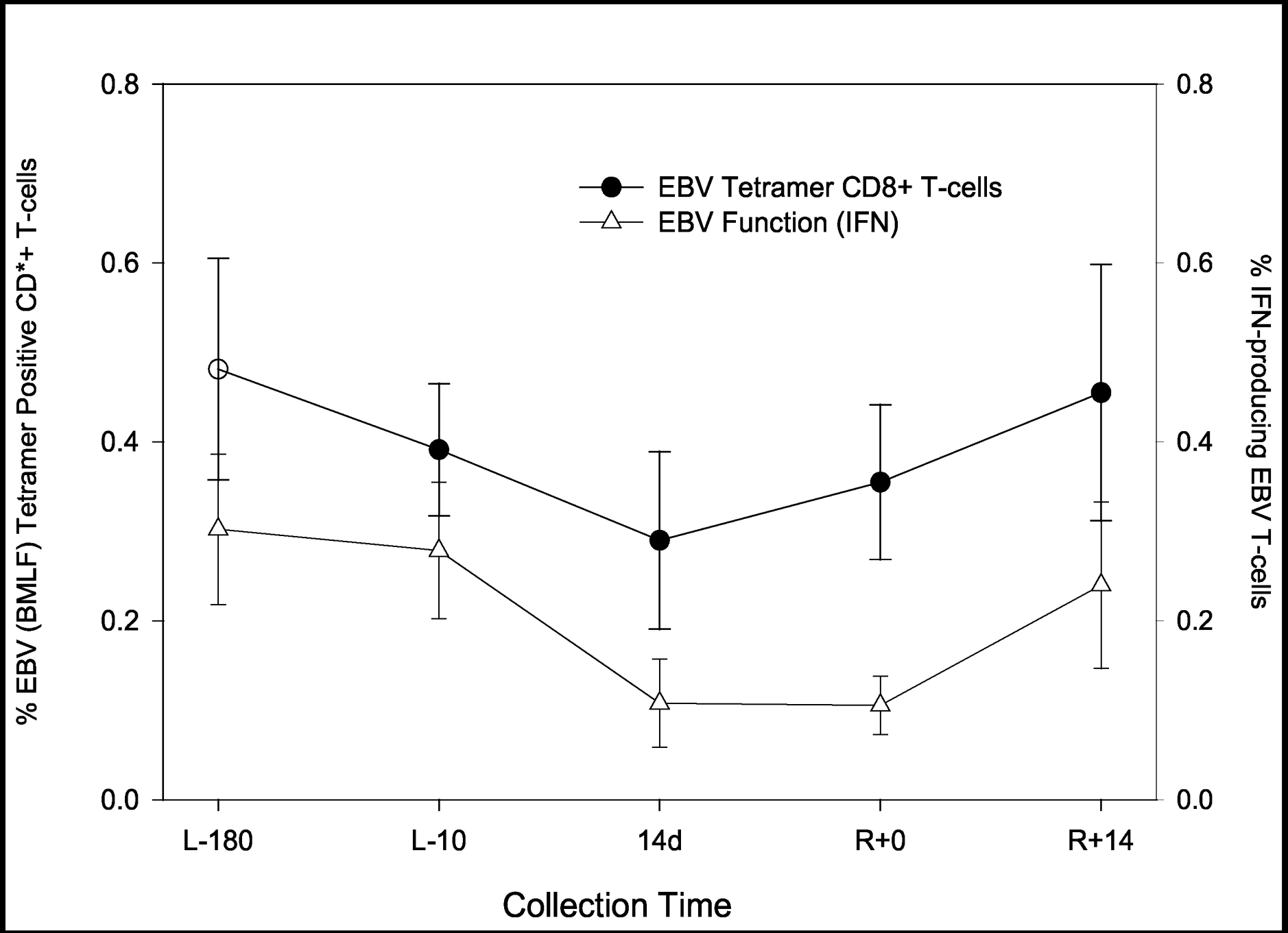
Viral Antibody Titers



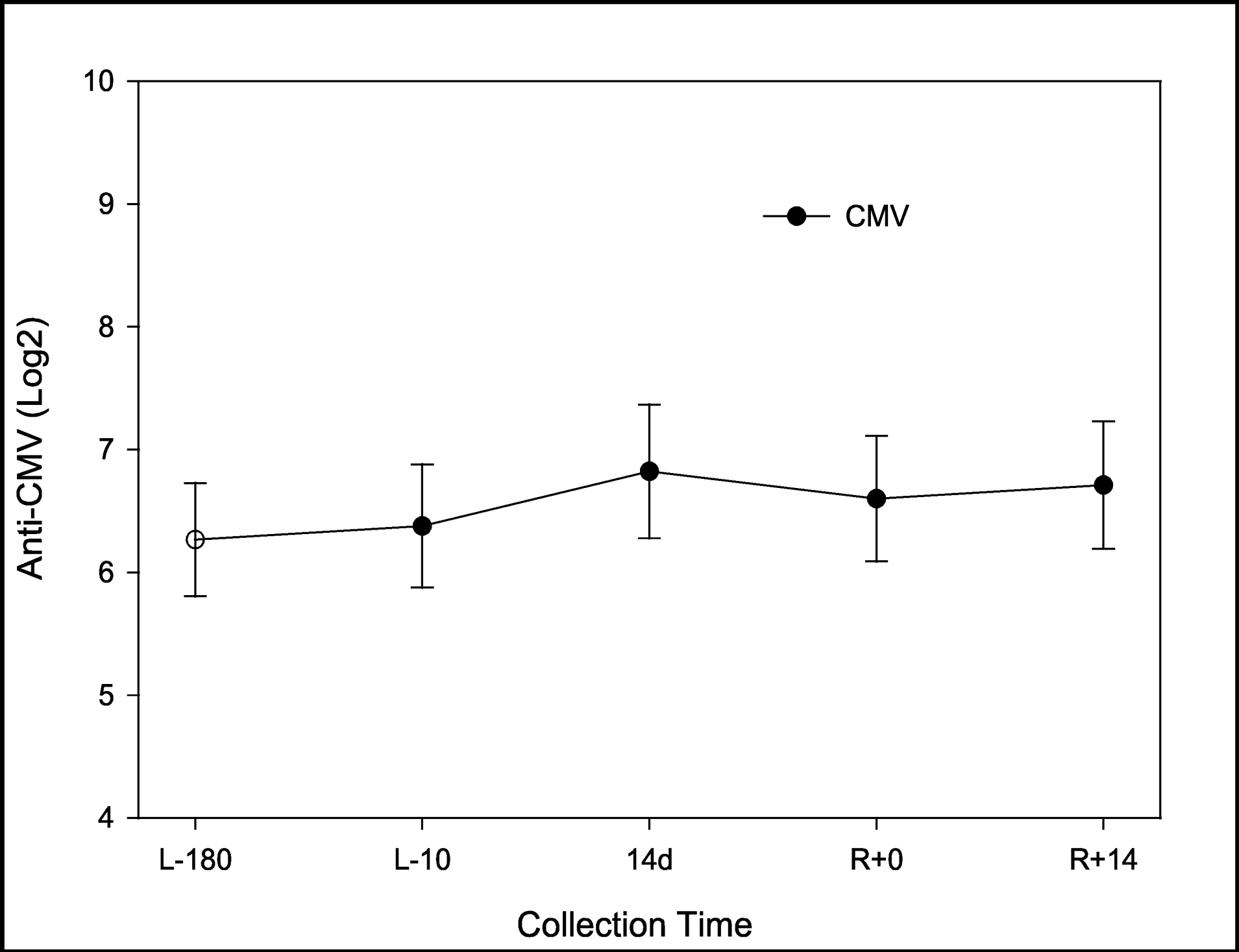
Viral Antibody Titers



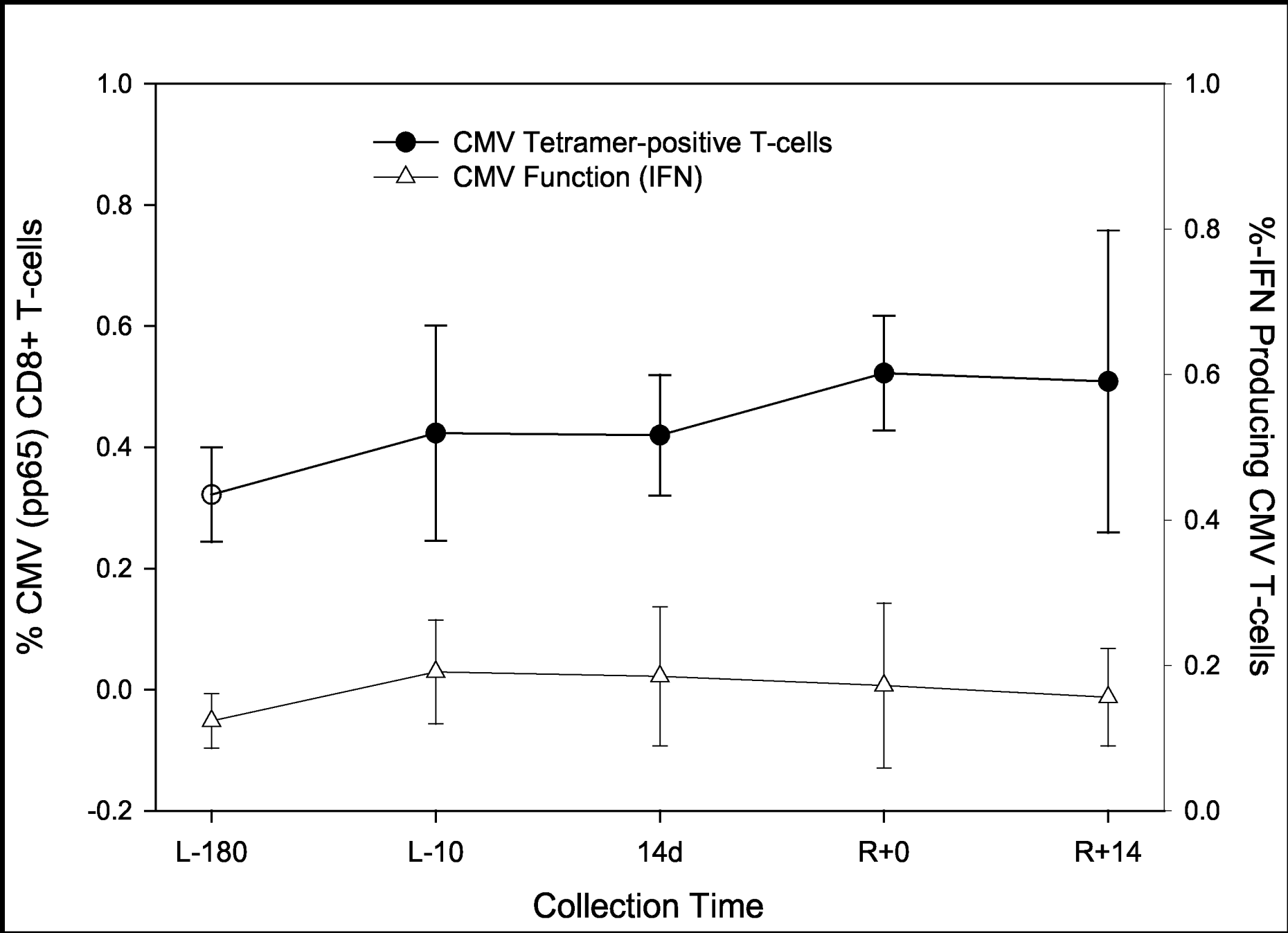
Virus-specific T cell Number/Function



Viral Antibody Titers

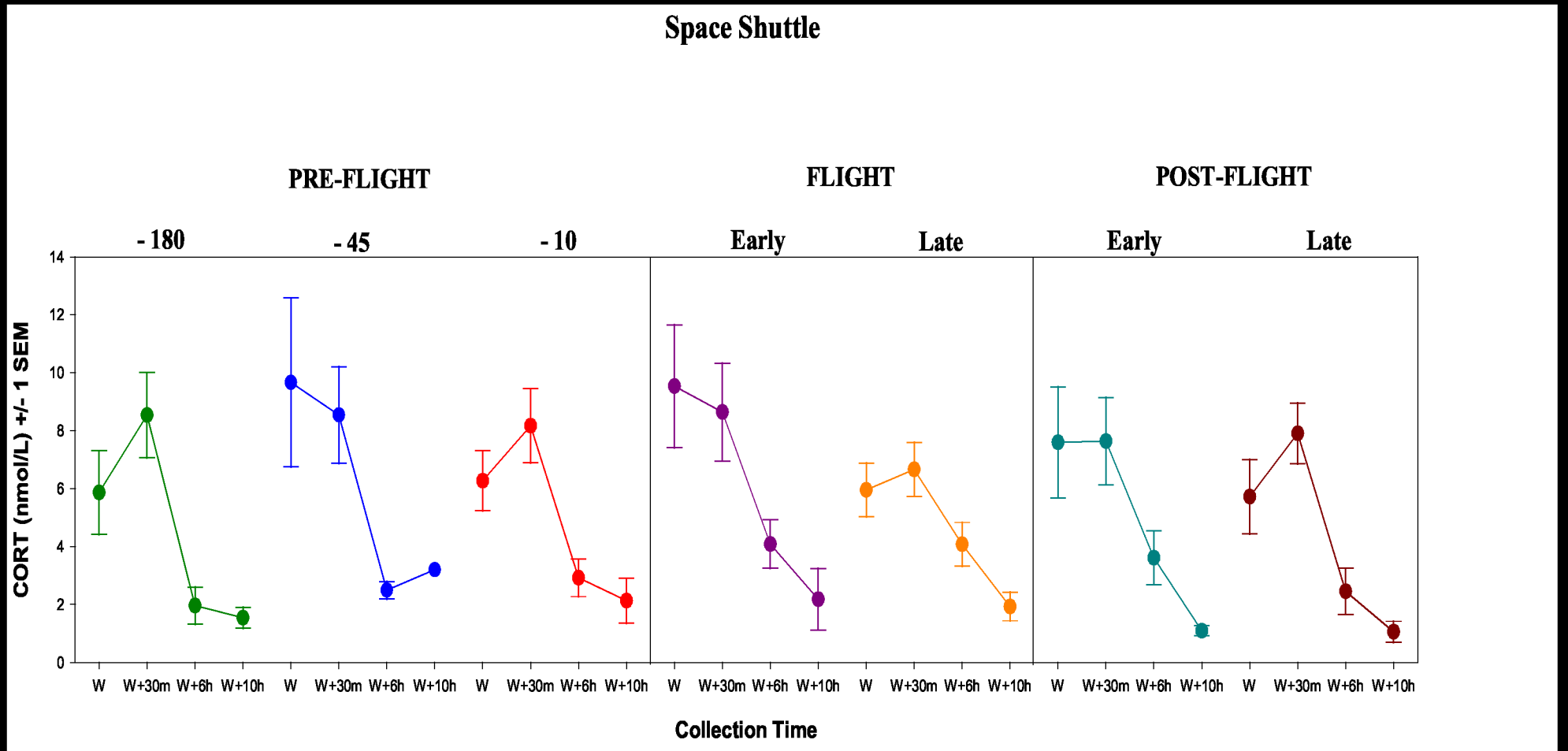


Virus-specific T cell Number/Function



JSC Microbiology Laboratory

-Latent herpesvirus reactivation (EBV, CMV, VZV)
-Stress hormone levels (saliva/urine)
-Circadian rhythm analysis.



Sample Size (n = 11)

Viral Reactivation in Short Duration Space Flight

Total number of crewmembers	**17**
Male	**16**
Female	**1**
Number of space flights	**9**

EBV, VZV and / or CMV shedding in 17 Crewmembers

	Number of crewmembers who shed		
Total	**EBV**	**VZV**	**CMV**
17	14	7	8
	pre, during or post	both during and post	pre, during or post

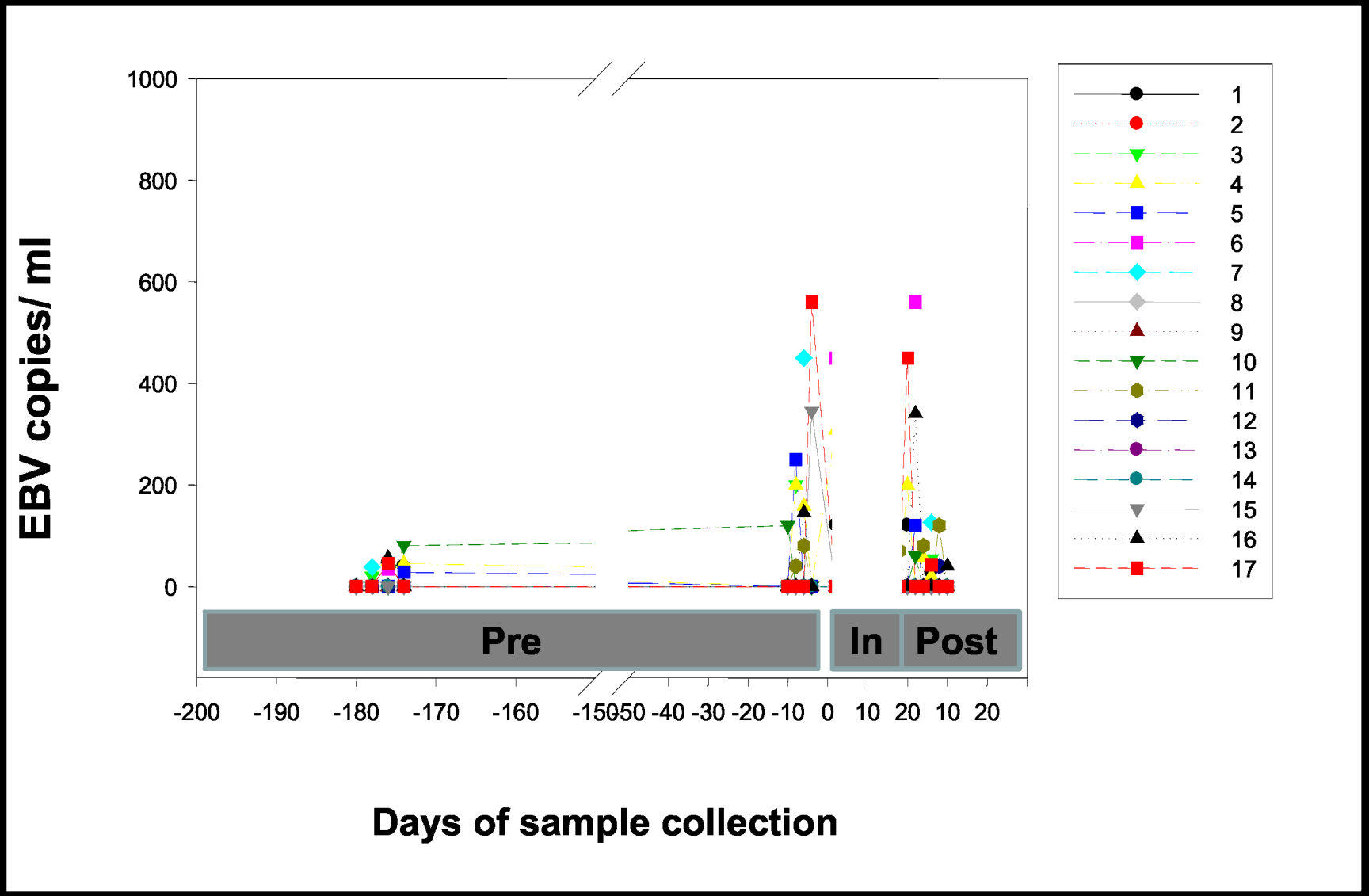
No EBV in 3 / 17 subjects
No VZV in 10 / 17 subjects
No CMV in 9 / 17subjects

There were 3 subjects who did not shed any of the three viruses tested.

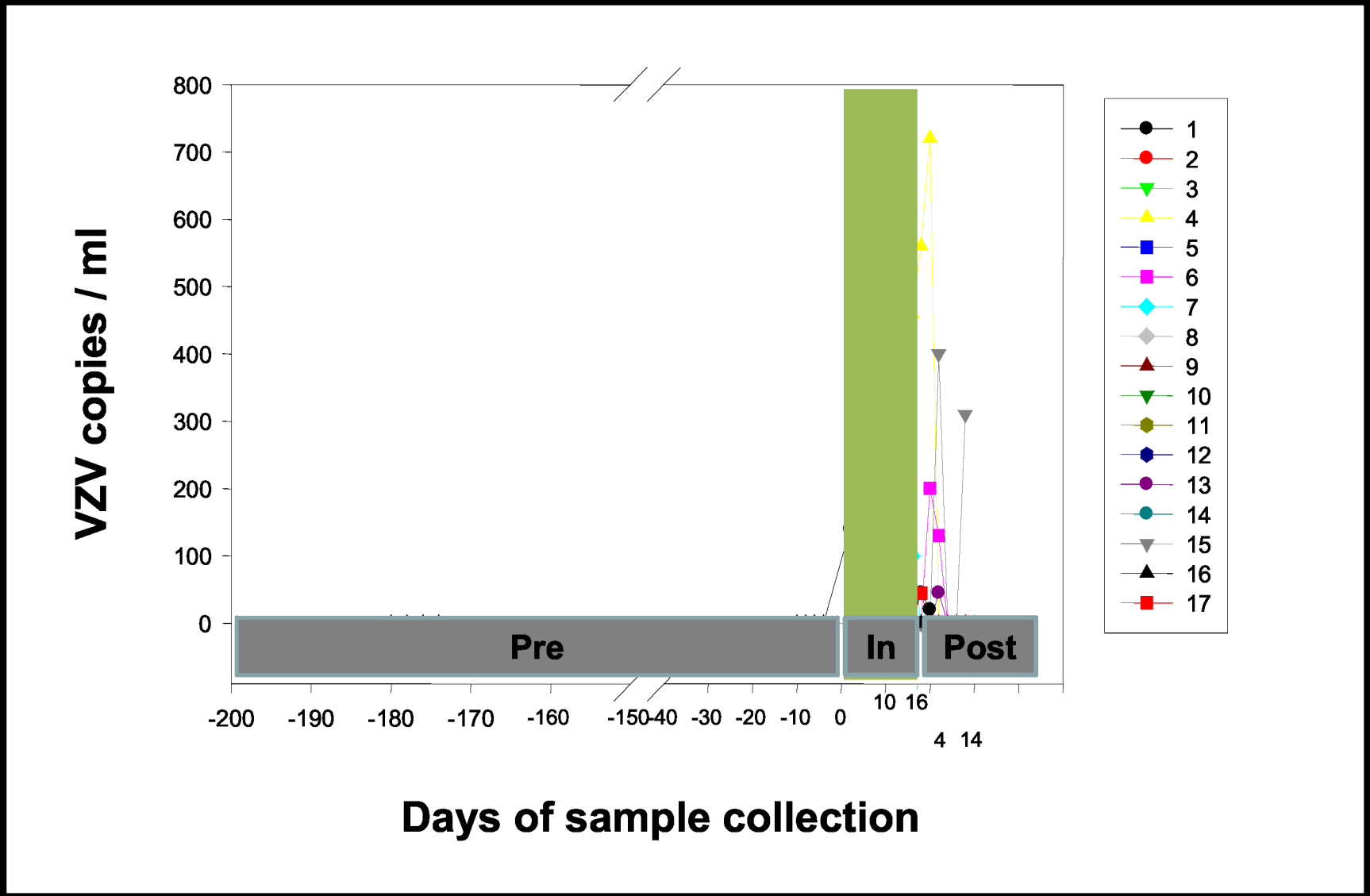
EBV, VZV and CMV in 17 short duration crewmembers' saliva and urine samples before, during and after the space flight

	Total samples	Pre	During	After
Number of saliva samples collected	**381**	**136**	**137**	**78**
Samples positive for EBV	72	22	32	18
%	18.9	16.2	23.4	23.1
Samples positive for VZV	28	0	22	6
%	7.4	0	16.0	7.7
Number of urine samples collected	66	34	0	32
Samples positive for CMV	21	6	0	14
%	31.8	17.7	0	43.8

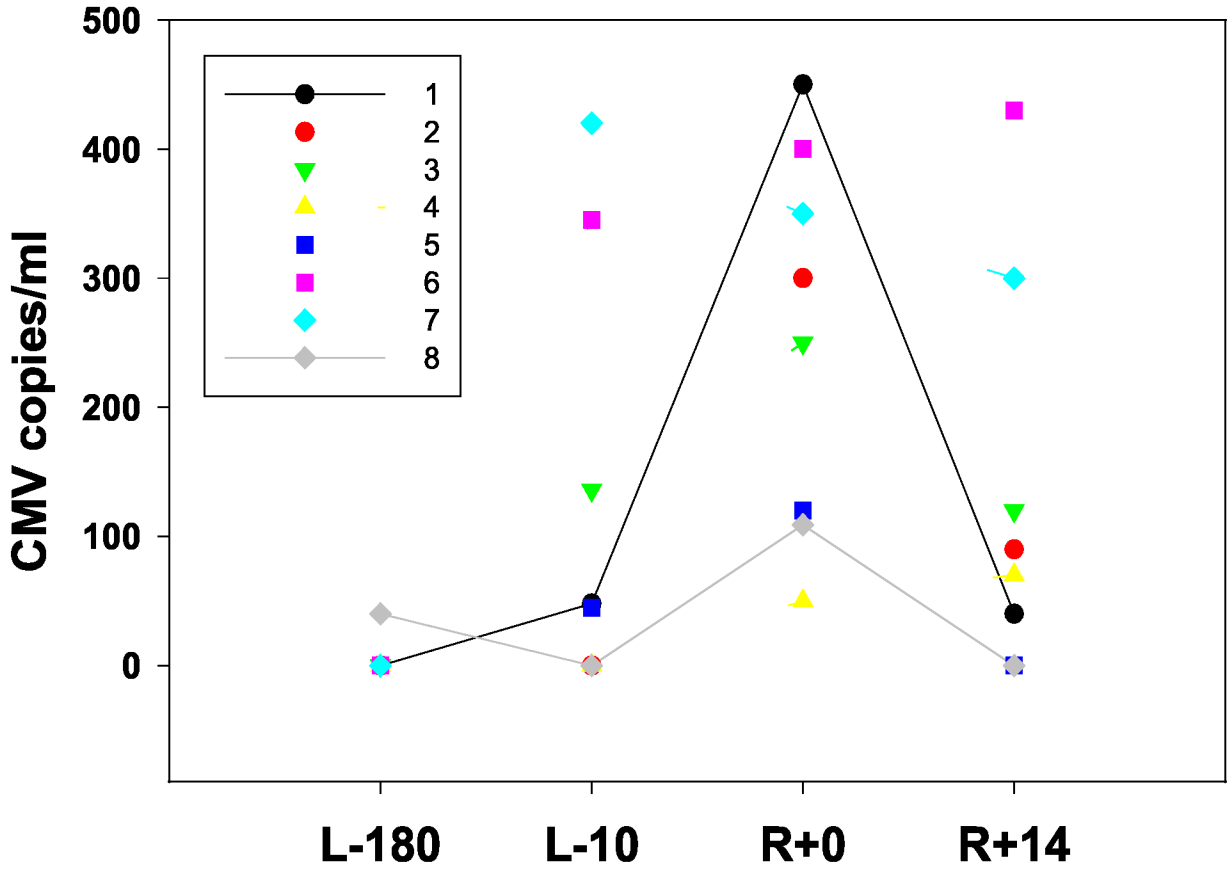
Salivary EBV in 17 short duration crewmemebers



Salivary VZV in 17 short duration crewmemebers



Urinary CMV DNA copies in 8 space shuttle crewmembers



Next Step…

- ISS/long duration portion will determine if these alterations persist or resolve over course of 6 month orbital flight.

- Resolved changes would indicate short duration findings related to high activity/high stress environment of Space Shuttle mission.

- Persistent phenomenon may support countermeasures development.